September 6, 2002

Anne P. LeHuray, Ph.D.
Technical Contact
American Chemistry Council
Rubber and Plastic Additives Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. LeHuray:

The Office of Pollution and Toxics is transmitting EPA's comments on the robust summaries and test plan for Benzothiazole-based Thiazoles Category, posted on the ChemRTK HPV Challenge Program Web site on December 20, 2001. I commend The American Chemistry Council's Rubber and Plastic Additives Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The American Chemistry Council's Rubber and Plastic Additives Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

*-S-*

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

**EPA Comments on Chemical RTK HPV Challenge Submission:**

**Benzothiazole-based Thiazoles Category**

## SUMMARY OF EPA COMMENTS

The sponsor, the Rubber and Plastic Additives (RAPA) Panel of the American Chemistry Council, submitted a test plan and robust summaries to EPA for the Benzothiazole-based Thiazoles Category dated November 30, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 20, 2001. The category includes the four sponsored chemicals: 2-(morpholinodithio)-benzothiazole (MORFAX), 2(3H)-benzothiazolethione (2-mercaptobenzothiazole, MBT), 2(3H)-benzothiazolethione, zinc salt (ZMBT), and 2(3H)-benzothiazolethione, sodium salt (NaMBT); and two analogous supporting chemicals, benzothiazole (BTH) and 2,2'-dithiobis-benzothiazole (MBTS).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. EPA disagrees with the submitter that these chemicals constitute a single category. The submitter needs to discuss the anticipated regular pattern or similarity in the properties for the members of the category. The submitter also needs to provide a description of why the supporting analogs were chosen and how the available data for these analogs relate to the sponsored chemicals. For health and ecological effects, the submitter needs to provide justification for the conclusion that MBT, NaMBT, and ZMBT have similar toxicities, that MBTS and MORFAX behave similarly, and that the data from MBT and MBTS can be extrapolated to the appropriate members of the category.

2. Physicochemical Properties and Environmental Fate. The submitter needs to provide measured melting point, boiling point, vapor pressure, and water solubility data for NaMBT, ZMBT, and MORFAX. The submitter needs to provide measured stability in water data for ZMBT and MORFAX, and measured biodegredation data for MORFAX.

3. Health Effects. For the purposes of the HPV Challenge Program, adequate data are available on all health effects endpoints for MBT and on acute toxicity and mutagenicity for all chemicals except for mutagenicity for MORFAX. The submitter proposes no additional testing for the members of this category. However, the submitter needs to provide an adequate category justification for health effects as stated under item #1 above. The submitter also needs to address deficiencies in the submitted robust summaries.

4. Ecological Effects. Some required data elements were missing for MBT and NaMBT on all three ecological endpoints (fish, daphnid, and algae), and EPA reserves judgement on the adequacy of these studies pending submission of missing data elements. Also, the submitted data on ZMBT and MORFAX are inadequate for all ecotoxicity endpoints. Furthermore, there is no SAR chemical class validated for these chemicals in ECOSAR. EPA therefore recommends for ZMBT acute testing in fish, invertebrates, and algae or, depending on the stability in water test results, chronic invertebrate testing, using measured concentrations and identifying the tested product(s) analytically. Depending on the test results for water solubility and stability in water, the same approach may be necessary for MORFAX.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

**EPA COMMENTS ON THE BENZOTHIAZOLE-BASED THIAZOLES CATEGORY CHALLENGE SUBMISSION**

## Category Definition

The sponsor proposes a category containing four sponsored chemicals and two analogs. The four sponsored chemicals are 2-mercaptobenzothiazole (MBT, CAS No. 149-30-4), sodium 2-mercato-benzothiazole (NaMBT, CAS No. 2492-26-4), zinc 2-mercaptobenzothiazole (ZMBT, CAS No. 155-04-4) and 2-(4-morpholinyldithio)benzothiazole (MORFAX, CAS No. 95-32-9). The data on two analogs, benzothiazole (BTH, CAS No. 95-16-9) and benzothiazoledisulfide (MBTS, CAS No. 120-78-5), have been included to support the category. These chemicals consist of benzothiazole with various substitutents or hydrogen (BTH) at the 2-position.

In the test plan cover letter, the submitter differentiates between the sponsored chemicals and the two non-sponsored analog chemicals. In the test plan itself, however, this information appears only in table footnotes and readers are likely to infer initially that all six compounds shown are sponsored category members. The submitter needs to add the explanation in the cover letter to the test plan.

## Category Justification

The submitter's primary justification for the category is the structural similarity of the category members and the expectation that the 2-mercaptobenzothiazole functional group will be the major determinant of the physicochemical, environmental, and toxicological properties of these compounds.

However, the test plan discussion and data do not support the submitter's conclusions. EPA believes that close structural similarities and consistent data for MBT and NaMBT support grouping MBT, its sodium salt, NaMBT, and possibly its zinc salt, ZMBT. The submitter does not present evidence showing that ZMBT's zinc-sulfur bond behaves more ionically than covalently. In the absence of data demonstrating the dissociation of ZMBT, one cannot conclude that MBT and ZMBT will have similar toxicities. As for MORFAX, the morpholinyldisulfide functional group may result in significantly different physicochemical, environmental, and toxicological properties compared to the other category members. The test plan does not address how MORFAX compares to the other category members, and supporting data for such a relationship are limited. The submitter states on page 3 of the test plan that all of the members hydrolyze and/or dissociate to MBT. This conversion is not obvious in the case of MORFAX, which is most susceptible to cleavage at the S-N bond, or MBTS, which requires reduction rather than hydrolysis to accomplish S-S cleavage. More discussion and supporting data are needed on this point. The submitter also needs to discuss how the data for MBTS are applicable to MORFAX. In addition, any potential impacts of the morpholine portion of the molecule on the toxicokinetics and toxicity of MORFAX need to be discussed.

For ecological effects, the submitter has used the calculated values from ECOSAR to fill the data gaps. However, there is no SAR chemical class validated for these chemicals in ECOSAR.

Finally, no discussion was provided to support the use of the BTH and MBTS data to group these chemicals in a category or to address data gaps.

**Test Plan**

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The submitter provided calculated data for melting point, boiling point, and vapor pressure for NaMBT, ZMBT, and MORFAX. Estimated values for these endpoints are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured data for these endpoints and use these data as inputs to the transport-distribution model. Measured data may be available from published sources.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

*Photodegradation*. The photodegradation data provided by the submitter are adequate for the purposes of the HPV Challenge Program.

*Stability in water*. On page 4 of the test plan, the submitter indicates that additional data collection efforts are not necessary for this endpoint. This conclusion is based on hydrolysis data for MBT and MBTS. The submitter presented two conflicting results for the hydrolysis of MBT (15 % and 0 % after 7 days). The submitter needs to clarify this discrepancy. Also, the submitter needs to provide measured stability in water data for ZMBT and MORFAX to support the claim that MBT is formed when ZMBT and MORFAX undergo hydrolysis.

*Biodegradation*. EPA disagrees with the submitter's suggestion that MORFAX would have similar biodegradation properties as MBTS. These two compounds are not structurally similar enough that the experimental data for one can be used to predict biodegradation for the other. Therefore, the submitter needs to provide measured ready biodegradation data for MORFAX following OECD guidelines.

*Transport and Distribution (fugacity)*. EPA disagrees with the submitter's conclusion that the requirement for this endpoint has been addressed and that no additional testing is necessary. The submitter used default input values in its transport and distribution model. The submitter needs to provide measured data as inputs to the transport-distribution model. The use of estimated default values introduces uncertainties that then become magnified in modeling applications.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

For the purposes of the HPV Challenge Program, adequate data are available on all health effects endpoints for MBT and MBTS and acute toxicity and mutagenicity data on all chemicals except for mutagenicity data on MORFAX. The submitter proposes no additional testing for the members of this category. However, the submitter needs to provide adequate justification in the test plan to support the conclusion that MBT, NaMBT, and ZMBT have similar toxicities, that MBTS and MORFAX may behave similarly, and that the data from MBT and MBTS can be extrapolated to the appropriate members of the category. The submitter also needs to address deficiencies in the submitted robust summaries.

*Acute Toxicity*. Several summaries for acute toxicity have been included in the IUCLID summary, and as all have consistent $LD_{50}$ values of greater than 2 g/kg, EPA considers the existing data adequate.

Ecological Effects (fish, invertebrates, and algae).

For both MORFAX and ZMBT, the calculated values are not acceptable because there is no SAR chemical class validated for these chemicals in ECOSAR.

*Fish, Invertebrate, and Algae.* Inadequate data exist for two sponsored category members, MORFAX and ZMBT. EPA recommends acute testing of ZMBT in fish, invertebrates, and algae, or, depending on

stability in water test results, chronic testing in invertebrates, in either case using measured concentrations and identifying the tested product(s) analytically. The same approach may be necessary for MORFAX, depending on the test results for water solubility and stability in water. For chemicals with log P values of $4.2 chronic testing may be needed. For more information and guidance pertaining to difficult-to-test substances and chemicals with high log P values refer to the OECD Web site at http://www.oecd.org/oecd/pages/home/displaygeneral/0,3380,EN-document-524-14-no-no-5745-0,00.html.

Some required data elements were missing for MBT and NaMBT on all three ecological endpoints (fish, daphnid, and algae), and EPA reserves judgement on the adequacy of these studies pending submission of missing data elements.

## Specific Comments on the Robust Summaries

### Health Effects

Robust summaries were typically missing necessary details, such as strain, sex, number of animals, vehicle, test substance information, methodological details, and extent of assessment of toxicological endpoints.

### Ecotoxicity

The missing data elements in robust summaries were pH, DO, water hardness, temperature, amount of solvent (acetone) used, purity of test substance, number of organisms tested, concentrations tested, test conditions, statistical methods used, GLP compliance, and test procedure.

## Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.